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REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing claim amendments are respectfully requested.

Claim 1 has been amended to define the invention with additionally clarity. Claim 4 has been amended to delete reference to the possibility of A being a stable, non-cytotoxic species. Claim 6 has been amended to revise the definition of Z so that it encompasses all of the possibilities for Z in dependent claims 7 and 8 for the case where n is 0. Claims 7 and 8 have been amended for consistency with claim 6. That the claims have been revised should not be construed as an indication that Applicants agree with any view expressed by the Examiner. Rather, the revisions are made merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

As pointed out in the Response filed April 19, 2006, the present invention relates to bioreductive drug conjugates for use in targeting of therapeutic agents to localized regions of hypoxic and/or ischemic tissue within the body. The conjugates comprise a bioreductive moiety linked to a therapeutic agent. At a hypoxic/ischemic site, the bioreductive moiety undergoes bioreduction to generate release of the therapeutic agent which has therefore been targeted to the hypoxic ischemic site.

It is an important feature of the invention that the residue of the bioreductive moiety (i.e. after bioreduction thereof) is non-cytotoxic and in particular does not undergo reaction with biomolecules. The application as filed describes two "mechanisms" by which it may be ensured that the reduced form of the bioreductive moiety does not undergo reaction with a biomolecule. One such mechanism is disclosed in general terms at page 6, lines 9-18, of the specification and

is based on the feature that, on bioreduction of the bioreductive moiety (to effect release of the therapeutic agent), the original bioreductive moiety gives rise to a self-alkylating species so that there is an <u>intramolecular</u> alkylation reaction within said species which occurs in preference to alkylation of any biomolecule such as DNA. Claim 1 is directed to this feature.

A further "mechanism" disclosed in the application for generating a non-cytoxic residue of the bioreductive moiety is as discribed in the paragraph bridging pages 6 and 7 of the specification. In this embodiment, the bioreductive moiety is such that, on bioreduction (to release the therapeutic agent), there is generated an alkylating center which is sterically hindered thus abolishing alkylating reactivity and preventing alkylation of biomolecules. This is the subject of independent claim 18.

Claims 1-25 stand rejected under 35 USC 102(b) as allegedly being anticipated by Firestone et al. The rejection is traversed.

Firestone et al discloses a compound comprising a bioreductive moiety (a nitro-quinoline) linked to a therapeutic agent (phosphoramide mustard (PDA)). In the presence of hypoxic tissue, the nitro-quinoline undergoes bioreduction with consequential elimination of PDA (see Scheme I at the top of page 2934 of Firestone et al).

The "remnant" of the bioreductive moiety (i.e., after release of the PDA) is shown as being a quinoline salt in which the nitrogen atom of the quinoline is positively charged and the quinoline residue has an aliphatic chain incorporating a double bond. (The structure of the salt is shown as the product of Scheme I). This product would not be capable of undergoing an self-alkylation reaction (that is, an intramolecular alkylation reaction) as required by claim 1 nor does it incorporate a sterically hindered alkylating center (see claim 18). Stated otherwise, there are no groups in the product of Scheme I of Firestone et al that could react intramolecularly.

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In support of the rejection, the Examiner refers to compound 6 of Firestone et al. This is the product of Scheme II which shows the synthesis of a compound (i.e., compound 6) that is similar to the compound I in Scheme I. Compound 6 differs from compound I in that the former has a 6-(dimethylamino)methyl group as a solubilizing group (see also the first few lines of the section entitled "Chemistry" in the right hand column of page 2934 of Firestone et al). The Examiner argues that bioreduction of compound 6 would form a 3-(6-dimethylaminomethyl-3-amino-quinolin-8-yl)-acrylic acid on bioreduction (effectively, this would be the equivalent of the product of Scheme I). The Examiner goes on to make the point that this moiety (i.e., the product of bioreduction) could react with a second molecule thereof (i.e., dimerization). The Examiner may or may not be correct (certainly there is no suggestion in Firestone et al that the product of Scheme I undergoes dimerization) but, that aside, there is no self-alkylation reaction as required by the instant invention. Put another way, dimerization is not an intramolecular reaction.

In view of the above, reconsideration and withdrawal of the rejection are requested.

Claims 1-25 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

At the outset, it is noted that the Examiner offers no basis for his assertion that the referenced terms are indefinite. Further, the Examiner's assertion that the terms lack clarity overlooks the fact that these terms are widely used in the art. Further, the subject specification provides definitions that the Examiner may have overlooked.

More specifically, the Examiner's attention is directed to the definitions given in the final two paragraphs on page 4 of the specification, particularly with reference to the term "non-

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cytotoxic bioreductive moiety". The word "cytotoxic" has a well understood meaning as does

"bioreductive", which is in fact the first word of Firestone et al.

The term "therapeutic agent" is commonly used in the relevant art and does not lack

clarity.

With regard to "bioreduction" see comments above relating to "bioreductive". It should

also be noted that the documents listed on the Information Disclosure Citation sheet returned

with the Office Action lists a number of papers which, in their title, use "bioreductive" or similar

term (see particularly the Mehta et al, Chikhale et al and Berglund references).

Further definition relating to the term "species having an alkylating centre...self-

alkylating reaction" is provided on page 6 of the present specification.

Given that the terms noted by the Examiner are "terms of art", no revision is believed

necessary and reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect

is requested.

Respectfully submitted,

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